Why Do Some Older Adults Treated With Antidepressants Progress to Dementia?

Eric E. Brown, MD, MSc, FRCPC; Tarek K. Rajji, MD, FRCPC; and Benoit H. Mulsant, MD, MS, FRCPC

The relationship between a history of depression and incident dementia is well established, yet incompletely understood. A history of remote or recent depression is associated with a 2-fold higher risk of incident dementia. Despite large studies designed to elucidate the mechanism underlying this epidemiologic relationship, it is still not clear whether depression is a causal contributor to dementia, a disorder with common risk factors, or a symptom of an underlying neurodegenerative process and a prodrome of dementia. This uncertainty is due in large part to the complexity of these two clinical syndromes, each with heterogeneous etiologies, pathophysiologies, and treatments, all of which can interact with biopsychosocial factors across individuals and populations. Thus, a given individual with depression may progress from depression to dementia due to one, all, or none of the above mechanisms.

Because antidepressant medications are effective (although not when dementia is already present), their use may help to understand the dementia-depression relationship. If depressive episodes causally contribute to the development of dementia, their successful treatment should lower the risk of dementia compared to untreated episodes. However, antidepressants are heterogeneous, with broad biological effects. They can directly or indirectly impact the overlapping physiologic changes observed in depression and dementia, including neuroinflammation, neurovascular factors, neurotrophic factors, or the metabolism of amyloid-β and tau protein. Thus, antidepressants could increase or decrease the risk of dementia, independent of their effect on depression.

In their article, Bartels et al report on a study of the relationship between antidepressant use and risk of incident dementia conducted in the context of preexisting conflicting studies. While most studies published to date have grouped antidepressants by class, and few have addressed the issue of treatment duration, their study addresses both of these potentially important factors. They used an observational, case-control design to retrospectively analyze data from a representative sample of 1,203 (3%) of the primary care practices in Germany. They identified 62,317 patients 65 years of age or older who received an incident diagnosis of dementia in 2013–2017. Dementia patients were matched with 62,317 control patients based on age, sex, individual primary care physician, and index year. Dementia patients and controls were compared based on whether they were prescribed 1 of 14 antidepressant pharmacotherapies at the index date: 5 selective serotonin reuptake inhibitors (SSRIs)—citalopram, escitalopram, fluoxetine, paroxetine, or sertraline; 2 serotonin-norepinephrine reuptake inhibitors (SNRIs)—duloxetine or venlafaxine; 4 tricyclic antidepressants (TCAs)—amitriptyline, doxepin, opipramol, or trimipramine; the herbal Hypericum perforatum; lithium; or mirtazapine. Regression models assessed the association between incident dementia and either prescription of antidepressants or duration of treatment. Covariates included a diagnosis of depression (to control for the association between a diagnosis of depression and receiving an antidepressant), severity of depression, diagnoses of other common medical disorders associated with dementia or antidepressant use (eg, diabetes or anxiety), and health insurance.

Depression was associated with incident dementia: 31% of patients had depression versus 24% of controls. Odds of incident dementia varied by medications classes: it was increased with SSRIs and SNRIs and decreased with TCAs. Citalopram was the most prescribed SSRI, and it was the only SSRI statistically associated with increased odds of dementia, as was mirtazapine. All TCAs and Hypericum perforatum independently decreased the odds of dementia. Duration of treatment was dichotomized as short- or long-term based on a median split of 710 days. Typically, long-term use was associated with a lower risk of incident dementia than short-term use. This was striking for escitalopram, for which short-term use was associated with an increased risk and long-term use with a decreased risk.

Bartels et al state that their covariates address confounding by indication because they include diagnoses and severity of depression (when available). However, their analysis does not account for some other important potential confounds, and we do not believe that confounding by indication has been ruled out. For example, physicians often choose...
Brown et al

It is illegal to post this copyrighted PDF on any website.

Published online: August 25, 2020.

Potential conflicts of interest: Dr Rajhi has received research support from Brain Canada, Brain and Behavior Research Foundation, BrightFocus Foundation, Canada Foundation for Innovation, Canada Research Chair, Canadian Institutes of Health Research, Centre for Aging and Brain Health Innovation, US National Institutes of Health (NIH), Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, and the Weston Brain Institute. He also received in-kind equipment support for an investigator-initiated study from Magstim and in-kind research accounts from Scientific Brain Training Pro. Dr Mulsant has received research financial support from Brain Canada, CAMH Foundation, Canadian Institutes of Health Research, and NIH; nonfinancial support from Pfizer (medication for an NIH-funded trial), Eli Lilly (medication and matching placebo for an NIH-funded trial), Capital Solution Design (software for a trial funded by the CAMH Foundation), and HAPPYneuron (software for a trial funded by Brain Canada). He directly owns shares of General Electric (less than $5,000). Dr Brown has no potential conflicts of interest to disclose.

Funding/support: None.

REFERENCES